Answer 1:

Bibliographic Information

The effects of various chemotherapy regimens on the expression of PCNA and Bcl-2 in human breast cancer xenograft (MCF-7) transplanted in nude mice. Wang, Yu-dong; Liu, Wei; Ji, Zhi-min; Zhang, Zhi-gang; Lv, Ya-lei; Wang, Shu-qin. Department of Medical Oncology, The 4th Hospital of Hebei Medical University, Shijiazhuang, Peop. Rep. China. Linchuang Zhongliuxue Zazhi (2007), 12(3), 173-176. Publisher: Institution of Chinese Clinical Oncology Journal, CODEN: LZZIA5 ISSN: 1009-0460. Journal written in Chinese. CAN 148:205626 AN 2007:1152600 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The objective of the paper is to investigate the effects of various chemotherapy regimens on the expression of PCNA and Bcl-2 of breast cancer, to assess the relationships between chemotherapy and two markers, and to evaluate the value of them to predict the response of chemotherapy. Forty-eight nude mice models of human breast cancer xenograft (MCF-7) were established, and then were randomly divided into control and 5 chemotherapy groups (each group, n = 8). Among 5 chemotherapy groups, mice were treated i.p. or orally by 5 chemotherapy regimens (CMF, CAF, NP, TP, Xeloda) resp. at two-thirds LD10 (dose lethal to 10% of the mice). Control animals were administered i.p. with normal saline. The pathol. feature of transplanted tumor was studied by HE stain, and the expression of Bcl-2 and PCNA was studied by SP immunohistochem. method. The expression of PCNA in 5 chemotherapy group was significantly lower than that of control ($P<0.05$), and the expression of PCNA in NP, TP and Xeloda groups was significantly lower than that of CMF and CAF groups ($P<0.05$). Moreover, the expression of PCNA was significantly correlated with pathol. therapeutic response ($P=0.001$). The expression of Bcl-2 in CAF, NP, TP, Xeloda groups was significantly higher than that of control ($P<0.05$). Moreover, the expression of Bcl-2 in TP group was significantly higher than that of CMF and CAF groups ($P<0.05$). The expression of Bcl-2 was not significantly correlated with the pathol. therapeutic response ($P=0.093$). Chemotherapy can increase the expression of PCNA, and decrease the expression of Bcl-2. Different chemotherapy regimens have different effects on PCNA and Bcl-2. PCNA can become a factor to evaluate the response to chemotherapy, and become possibly the prospective factor of chemoselect.

Answer 2:

Bibliographic Information

Synthesis and biological activity of stable branched neurotensin peptides for tumor targeting. Falciani, Chiara; Fabbrini, Monica; Pini, Alessandro; Lozzi, Luisa; Lelli, Barbara; Pileri, Silvia; Brunetti, Jlenia; Bindi, Stefano; Scali, Silvia; Bracci, Luisa. Department of Molecular Biology, Laboratory of Molecular Biotechnology, University of Siena, Siena, Italy. Molecular Cancer Therapeutics (2007), 6(9), 2441-2448. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 147:517195 AN 2007:1043801 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Receptors for endogenous regulatory peptides, like the neuropeptide neurotensin, are overexpressed in several human cancers and can be targets for peptide-mediated tumor-selective therapy. Peptides, however, have the main drawback of an extremely short half-life in vivo. We showed that neurotensin and other endogenous peptides, when synthesized as dendrimers, retain biol. activity and become resistant to proteolysis. Here, we synthesized the neurotensin functional fragment NT(8-13) in a tetrabranched form linked to different units for tumor therapy or diagnosis. Fluorescent mols. were used to monitor receptor binding and internalization in HT29 human adenocarcinoma cells and receptor binding in HT29 tumor xenografts in nude mice. Linking of chemotherapic mols. like chlorin e6 and methotrexate to dendrimers resulted in a dramatic increase in drug selectivity, uptake of which by target cells became dependent on peptide receptor binding. When nude mice carrying human tumor xenografts were treated with branched NT(8-13)-methotrexate, a 60% redn. in tumor growth was obsd. with respect to mice treated with the free drug.

Answer 3:

Bibliographic Information

Clinical and mechanistic aspects of glucocorticoid-induced chemotherapy resistance in the majority of solid tumors. Zhang, Chengwen; Wenger, Till; Mattern, Juergen; Ilea, Septimia; Frey, Christian; Gutwein, Paul; Altevogt, Peter; Bodenmueller, Wolfram; Gassler, Nikolaus; Schnabel, Philipp A.; Dienemann, Hendrik; Marme, Alexander; Hohenfellner, Markus; Haferkamp, Axel; Pfitzenmaier, Jesco; Groene, Hermann-Josef; Kolb, Armin; Buechler, Peter; Buechler, Markus W.; Friess, Helmut; Rittgen, Werner; Edler, Lutz; Debatin, Klaus-Michael; Krammer, Peter H.; Rutz, Hans P.; Herr, Ingrid. Research Group Molecular OncoSurgery, University of Heidelberg, Heidelberg, Germany. Cancer Biology & Therapy (2007), 6(2), 278-287. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 147:479951 AN 2007:1039338 CAPLUS

Abstract

Glucocorticoids have been used widely in conjunction with cancer therapy due to their ability to induce apoptosis in hematol. cells and to prevent nausea and emesis. However, recent data including ours, suggest induction of therapy-resistance by glucocorticoids in solid tumors, although it is unclear whether this happens only in few carcinomas or is a more common cell type specific phenomenon. We performed an overall statistical anal. of our new and recent data obtained with 157 tumor probes evaluated in vitro, ex vivo and in vivo. The effect of glucocorticoids on apoptosis, viability and cell cycle progression under diverse clin. important questions was examd. New in vivo results demonstrate glucocorticoid-induced chemotherapy resistance in xenografted prostate cancer. In an overall statistical anal. we found glucocorticoid-induced resistance in 89% of 157 analyzed tumor samples. Resistance is common for several cytotoxic treatments and for several glucocorticoid-derivs. and due to an inhibition of apoptosis, promotion of viability and cell cycle progression. Resistance occurred at clin. achievable peak plasma levels of patients under anti-emetic glucocorticoid therapy and below, lasted for a long time, after one single dose, but was reversible upon removal of glucocorticoids. Two nonsteroidal alternative anti-emetic agents did not counteract anticancer treatment and may be sufficient to replace glucocorticoids in cotreatment of carcinoma patients. These data demonstrate the need for prospective clin. studies as well as for detailed mechanistic studies of GC-induced cell-type specific pro- and anti-apoptotic signaling.

Answer 4:

Bibliographic Information

Effects of various chemotherapy regimens on the expression of PCNA and growth of human breast cancer xenograft (MCF-7) in nude mice. Wang, Yu-dong; Liu, Wei; Ji, Zhi-min; Zhang, Zhi-gang; Wang, Jun-ling; Yan, Xia; Zhang, Xiang-hong. Department of Medical Oncology, 4th Hospital, Hebei Medical University, Shijiazhuang Hebei, Peop. Rep. China. Zhongguo Aizheng Zazhi (2007), 17(2), 139-143. Publisher: Fudan Daxue Fushu Zhongliu Yiyuan, CODEN: ZAZHAF ISSN: 1007-3639. Journal written in Chinese. CAN 147:86596 AN 2007:395164 CAPLUS

Abstract

Although standardized therapy has been widely adapted in clin. practice and results are being improved, effective protocols for truly individualized chemotherapy is still lacking. The anti-tumor activity of different combination regimens on human breast cancer xenograft (MCF-7) transplanted in nude mice and their impacts on the expression of PCNA were investigated, and to evaluate the value of PCNA as predictive factors for the res. 88 Nude mice with human breast cancer xenograft (MCF-7) were randomly divided into control and 10 chemotherapy groups, and 8 mice were assigned into each group. Among 5 chemotherapy groups, they were treated either i.p. or orally by 5 different combinations of chemotherapy regimens (CMF, CAF, NP, TP, Xeloda) at one-third of LD10 dosage, and another 5 chemotherapy groups were treated at two-third . Control animals were given normal saline i.p. The body wt. of nude mice and transplanted tumor growth were recorded on a regular basis, and tumor growth inhibition was calcd. The pathol. features of the transplanted tumor were studied under the microscope before and after treatment. The expression of PCNA was evaluated by SP immunohistochem. method and flow cytometry. The results show that body wt. and tumor wt. of nude mice treated by two-third LD10 dosage of various chemotherapy combinations were significantly lower than that in the control ($P<0.05$), and the inhibition rate of tumor growth for the groups we. The results showed that the two-third LD10 dosage of chemotherapy could reflect the anti-tumor effect of various combinations chemotherapy better and more accurately, so this dosage was used for the next study. The expression at PCNA by immunohistochem. studies shows that the expression of PCNA in every chemotherapy group was significantly

lower than that of the control (P<0.05).
Moreover, the expressions of PCNA in NP group was significantly lower than that of CMF, CAF, TP and Xeloda group (P<0.05), while TP and Xeloda group was significantly lower than that of CMF and CAF group (P<0.05). FCM anal. shows that FI value of PCNA in every chemotherapy group was significantly lower than that of the control (P<0.05). FI value of PCNA in TP and Xeloda group was significantly lower than that of CMF and CAF group (P<0.05), while NP group a significantly lower than that of CMF group (P<0.05). Relationship between PCNA expression and pathol. response shows that the expression of PCNA was pos. correlated with pathol. therapeutic response of transplanted breast carcinoma (r=0.540, P<0.05). It was concluded that in vivo chemosensitivity testing with two third LD10 dosage of various combinations of chemotherapy cancer could somewhat predict the clin. situations. All of various chemotherapy regimens can decrease the expression of PCNA in breast cancer. The expression of PCNA could perhaps serve as the factor to judge the response to chemotherapy, and play a role in the selection of the kind of chemotherapy to be used in the clinic.

Answer 5:

Bibliographic Information

Colony-Stimulating Factor-1 Antibody Reverses Chemoresistance in Human MCF-7 Breast Cancer Xenografts. Paulus, Patrick; Stanley, E. Richard; Schaefer, Romana; Abraham, Dietmar; Aharinejad, Seyedhossein. Laboratory for Cardiovascular Research, Department of Anatomy and Cell Biology, Vienna Medical University, Vienna, Austria. Cancer Research (2006), 66(8), 4349-4356. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 144:404857 AN 2006:350676 CAPLUS

Abstract

Overexpression of colony-stimulating factor-1 (CSF-1) and its receptor in breast cancer is correlated with poor prognosis. Based on the hypothesis that blockade of CSF-1 would be beneficial in breast cancer treatment, we developed a murinized, polyethylene glycol-linked antigen-binding fragment (Fab) against mouse (host) CSF-1 (anti-CSF-1 Fab). Mice bearing human, chemoresistant MCF-7 breast cancer xenografts were treated with combination chemotherapy (CMF: cyclophosphamide, methotrexate, 5-fluorouracil; cycled twice i.p.), anti-CSF-1 Fab (i.p., cycled every 3 days for 14 days), combined CMF and anti-CSF-1 Fab, or with Ringer's soln. as a control. Anti-CSF-1 Fab alone suppressed tissue CSF-1 and retarded tumor growth by 40%. Importantly, in combination with CMF, anti-CSF-1 Fab reversed chemoresistance of MCF-7 xenografts, suppressing tumor development by 56%, down-regulating expression of the chemoresistance genes breast cancer-related protein, multidrug resistance gene 1, and glucosylceramide synthase, and prolonging survival significantly. Combined treatment also reduced angiogenesis and macrophage recruitment and down-regulated tumor matrix metalloproteinase-2 (MMP-2) and MMP-12 expression. These studies support the paradigm of CSF-1 blockade in the treatment of solid tumors and show that anti-CSF-1 antibodies are potential therapeutic agents for the treatment of mammary cancer.

Answer 6:

Bibliographic Information

An 19F magnetic resonance-based in vivo assay of solid tumor methotrexate resistance: proof of principle. Spees, William M.; Gade, Terence P. F.; Yang, Guangli; Tong, William P.; Bornmann, William G.; Gorlick, Richard; Koutcher, Jason A. Department of Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. Clinical Cancer Research (2005), 11(4), 1454-1461. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 143:19149 AN 2005:180829 CAPLUS

Abstract

Studies in oncol. have implicated multiple mol. mechanisms as contributors to intrinsic and acquired tumor resistance to antifolate therapy. Here we show the utility of an 19F-labeled methotrexate (FMTX) with 19F magnetic resonance to differentiate between sensitive and resistant tumors in vivo and thus predict therapeutic response. Human sarcoma xenografts in nude mice were used in this study. The sarcoma cell lines chosen for this study (HT-1080, HS-16, and M-805) are well characterized in terms of their

methotrexate sensitivity and mol. mechanisms of resistance. The pharmacokinetics of tumor uptake/washout of FMTX were monitored via in vivo 19F magnetic resonance spectroscopy (pulse/acquire with surface coil localization) following an i.v. bolus injection. Response post-therapy, following leucovorin rescue, was monitored via tumor growth. The three tumor models show differences in both the peak concns. of tumor FMTX and the dynamics of uptake/retention. These differences are most pronounced for time points late in the magnetic resonance observation period (225-279 min post-injection). A statistically significant linear correlation between tumor tissue concns. of FMTX at these late time points and therapeutic response in the days/wk post-treatment is shown ($R = 0.81$, $F = 9.27$, $P < 0.001$). Interestingly, a 400 mg/kg i.v. bolus injection of FMTX is a more potent cytotoxic agent in vivo against methotrexate-sensitive tumors than is the parent compd. ($P = 0.011$). In principle, the assay method described herein could be implemented in the clinic as a diagnostic tool to make decisions regarding therapeutic protocol for the treatment of osteosarcoma on a case-by-case basis.

Answer 7:

Bibliographic Information

Human osteosarcoma xenografts and their sensitivity to chemotherapy. Bruheim, Skjalg; Bruland, Oyvind S.; Breistol, Knut; Maelandsmo, Gunhild M.; Fodstad, Oystein. Department of Tumor Biology, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo, Norway. Pathology Oncology Research (2004), 10(3), 133-141. Publisher: Aranyi Lajos Foundation, CODEN: POREFR ISSN: 1219-4956. Journal written in English. CAN 142:253924 AN 2004:1018322 CAPLUS

Abstract

Despite the increased survival rates of osteosarcoma patients attributed to adjuvant chemotherapy, at least one third of the patients still die due to their disease. Further improvements in the management of osteosarcoma may rely on a more individualized treatment strategy, as well as on the introduction of new drugs. To aid in the preclin. evaluation of new candidate substances against osteosarcoma, we have established 11 human osteosarcoma xenograft lines and characterized them with regard to response to five different ref. drugs. Doxorubicin, cisplatin methotrexate, ifosfamide and lomustine were effective in 3/11, 3/11,1/10, 5/11 and 4/11 of the xenografts, resp. Five xenografts were resistant to all compds. tested. We also assessed the mRNA expression levels of the xenografts for the O6-Methylguanine DNA Methyltransferase (MGMT), DNA topoisomerase II- (Topo II)-α, Gluthathione-S-transferase (GST)-π, Multidrug-resistance related protein (MRP) 1 and Multidrug-resistance (MDR) 1 genes. There was an inverse correlation between the transcript levels of GST-π and doxorubicin growth inhibition ($r = -0.66$; $p<0.05$), and between the transcript levels of MGMT and the effect of lomustine ($r = -0.72$; $p<0.01$), whereas the expression of MRP1 and cisplatin growth inhibition was pos. correlated ($r=0.82$; $p<0.005$). This panel of xenografts should constitute a good tool for pharmacol. and mol. studies in osteosarcoma.

Answer 8:

Bibliographic Information

Intratumoral administration of methotrexate bound to activated carbon particles: Antitumor effectiveness against human colon carcinoma xenografts and acute toxicity in mice. Yuen, Nakase; Hagiwara, Akeo; Kin, Syuichi; Fukuda, Ken-ichirou; Ito, Tadao; Takagi, Tsuyoshi; Fujiyama, Jyunshin; Sakakura, Chohei; Otsuji, Eigo; Yamagishi, Hisakazu. Department of Digestive Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan. Journal of Pharmacology and Experimental Therapeutics (2004), 311(1), 382-387. Publisher: American Society for Pharmacology and Experimental Therapeutics, CODEN: JPETAB ISSN: 0022-3565. Journal written in English. CAN 141:343081 AN 2004:846874 CAPLUS

Abstract

We previously developed a new formulation of methotrexate (MTX) that is adsorbed onto a suspension of activated carbon particles (MTX-CH) and reported the usefulness of local administration in murine tumors. The present study examines the effects of human colon carcinoma (LoVo) xenografts and the acute toxicity of MTX-CH compared with MTX aq. soln. (MTX-AQ) in mice. In therapeutic expts., LoVo cells were implanted into the backs of BALB/c nude mice. When the cells had developed into tumors, we performed an

intratumoral administration of a weekly dose of 30 mg/kg. The MTX concn. in the tumor was compared between the MTX-CH group and MTX-AQ group. In expts. on acute toxicity, MTX-CH and MTX-AQ were injected s.c. in BDF1 mice, and intoxication symptoms, changes in body wt., and date of death were recorded. In the therapeutic expts., intratumoral administration of MTX-CH was much more effective in suppressing the tumor growth compared with MTX-AQ. In expts. of acute toxicity, the death time of the MTX-CH group was delayed to a greater extent, and the 50% LD (LD50) values of MTX-CH were lower than those of MTX-AQ. The LD50 values of MTX-CH are 75 times higher than the efficacious dose of 30 mg/kg. The present results suggest that intratumoral administration of MTX-CH is useful for local therapy and the therapeutic dose of MTX-CH can be safely injected s.c.

Answer 9:

Bibliographic Information

Genome-wide cDNA microarray screening to correlate gene expression profiles with sensitivity of 85 human cancer xenografts to anticancer drugs. Zembutsu, Hitoshi; Ohnishi, Yasuyuki; Tsunoda, Tatsuhiko; Furukawa, Yoichi; Katagiri, Toyomasa; Ueyama, Yoshito; Tamaoki, Norikazu; Nomura, Tatsuji; Kitahara, Osamu; Yanagawa, Rempei; Hirata, Koichi; Nakamura, Yusuke. Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo, Japan. Cancer Research (2002), 62(2), 518-527. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 136:395496 AN 2002:108259 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

One of the most crit. issues to be solved in regard to cancer chemotherapy is the need to establish a method for predicting efficacy or toxicity of anticancer drugs for individual patients. To identify genes that might be assocd. with chemosensitivity, we used a cDNA microarray representing 23,040 genes to analyze expression profiles in a panel of 85 cancer xenografts derived from nine human organs. The xenografts, implanted into nude mice, were examd. for sensitivity to nine anticancer drugs (5-fluorouracil, 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride, adriamycin, cyclophosphamide, cisplatin, mitomycin C, methotrexate, vincristine, and vinblastine). Comparison of the gene expression profiles of the tumors with sensitivities to each drug identified 1,578 genes whose expression levels correlated significantly with chemosensitivity; 333 of those genes showed significant correlation with two or more drugs, and 32 correlated with six or seven drugs. These data should contribute useful information for identifying predictive markers for drug sensitivity that may eventually provide "personalized chemotherapy" for individual patients, as well as for development of novel drugs to overcome acquired resistance of tumor cells to chem. agents.

Answer 10:

Bibliographic Information

Experimental therapeutics with a new 10-deazaaminopterin in human mesothelioma: Further improving efficacy through structural design, pharmacologic modulation at the level of MRP ATPases, and combined therapy with platinums. Khokhar, Nushmia Z.; She, Yuhong; Rusch, Valerie W.; Sirotnak, F. M. Program in Molecular Pharmacology and Experimental Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. Clinical Cancer Research (2001), 7(10), 3199-3205. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 137:41324 AN 2001:799808 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Studies described here sought to evaluate the therapeutic potential of a new 10-deazaaminopterin analog, 10-propargyl-10-deazaaminopterin (PDX), alone and in combination with platinum compds. in the treatment of human pleural mesothelioma. In vitro studies documented 25-30-fold and 3-fold, resp., greater cytotoxic potency of PDX compared with methotrexate and another 10-deazaaminopterin, edatrexate, against VAMT-1 and JMN cell lines derived from human mesothelioma. These tumor cell lines were also inhibited by platinum compds. Cisplatin (CDDP) was somewhat more inhibitory than oxaloplatin and >1 log order in magnitude more inhibitory than carboplatin (CBCDA). Against the JMN tumor xenografted in nude mice, whereas

methotrexate and, more so, edatrexate, were potently growth inhibitory, only PDX brought about substantial regression. By comparison, CDDP and CBCDA, but not oxaloplatin were markedly growth inhibitory to this same tumor in vivo. This high level of therapeutic activity of PDX could be addnl. enhanced by coadministration of probenecid, an inhibitor of canicular multispecific org. anion transporter/multidrug resistance-related protein (MRP)-like ATPases, which increased the no. of complete regressions by >-3 fold. Canicular multispecific org. anion transporter/MRP genes, primarily 1, 3, 4, 5, and 7, were in fact expressed in these human mesothelioma cell lines as detd. by real-time reverse transcription-PCR. These same MRP genes, including, to a lesser extent, MRP-4, were also expressed in pleural mesotheliomas derived from patients as shown by the same methodol. When combined with CDDP or CBCDA, PDX achieved 2-fold greater overall regression of the JMN tumor with a 3-4-fold increase in complete regressions, although some attenuation of dosages of each were required in the combination. These results strongly suggest that PDX has significant potential in the treatment of human pleural mesothelioma, particularly when coadministered with probenecid or combined with platinum compds.

Answer 11:

Bibliographic Information

Development of human lymphoma/leukemia xenograft models in immune-deficient mice for evaluation of potential anticancer agents. Dykes, D. J.; Hollingshead, M. G.; Camalier, R. F.; Waud, W. R.; Mayo, J. G. Southern Research Institute, Birmingham, AL, USA. Contributions to Oncology (1999), 54(Relevance of Tumor Models for Anticancer Drug Development), 295-304. Publisher: S. Karger AG, CODEN: COONEV ISSN: 0250-3220. Journal written in English. CAN 133:217399 AN 2000:242563 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Eleven human lymphoma/leukemia cell lines were assessed as in vivo xenograft models in severe combined immunodeficient (SCID) mice. In prepn. for efficacy evaluations of new antitumor agents, all eleven cell lines have been characterized for sensitivity to known clin. useful agents. The lines included in the study represent a variety of diseases including T-cell, myelogenous, and lymphoblastic leukemias, as well as histiocytic, B-cell and Burkitt's lymphomas. The selected agents for this study were representative of various chem. classes. Addnl., growth studies were performed including comparisons in athymic nude mice. These studies were designed to det. s.c. tumor vol. doubling times, graft success, latent growth periods, and other characteristics necessary to effectively implement and interpret anticancer efficacy evaluations. The various tumor lines used proved to be good models for chemotherapy trials. In the chemotherapy trials, considerable independent chemotherapeutic profiles were obsd. but there were also some similarities among the various histol. types.

Answer 12:

Bibliographic Information

MTA (LY231514) in combination treatment regimens using human tumor xenografts and the EMT-6 murine mammary carcinoma. Teicher, Beverly A.; Alvarez, Enrique; Liu, Pocheng; Lu, Ku; Menon, Krishna; Dempsey, Jack; Schultz, Richard M. Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, USA. Seminars in Oncology (1999), 26(2, Suppl. 6), 55-62. Publisher: W. B. Saunders Co., CODEN: SOLGAV ISSN: 0093-7754. Journal written in English. CAN 131:125026 AN 1999:290814 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

An important component in the development of a new anticancer drug is an understanding of its potential for inclusion in combination treatment regimens. LY231514, a multitargeted antifolate (MTA), was tested in combination with cisplatin, methotrexate, 5-fluorouracil, paclitaxel, docetaxel, doxorubicin, LY329201 (a glycinamide ribonucleotide formyl-transferase [GARFT] inhibitor), and fractionated radiation therapy in vivo using EMT-6 mammary carcinoma, human HCT 116 colon carcinoma, and human H460 non-small cell lung carcinoma grown as xenografts in nude mice. Isobologram methodol. was used to det. the additivity or synergy of the combination regimens. MTA administered with cisplatin, paclitaxel, docetaxel, or fractionated radiation therapy produced additive to greater than

additive tumor response by tumor cell survival assay and tumor growth delay. While an additive tumor response was obsd. when MTA was administered with methotrexate, synergistic tumor responses were seen when MTA was administered with the GARFT inhibitor, LY329201, or with the topoisomerase I inhibitor, irinotecan. MTA was administered in combination with full doses of each anticancer agent studied, with no evidence of increased toxicity resulting from the combination.

Answer 13:

Bibliographic Information

Pharmacokinetic optimization of the treatment of cancer with high dose zidovudine. Danesi, Romano; Falcone, Alfredo; Conte, Pier Franco; Del Tacca Mario. Division of Pharmacology and Chemotherapy, Department of Oncology, University Hospital, Pisa, Italy. Clinical Pharmacokinetics (1998), 34(2), 173-180. Publisher: Adis International Ltd., CODEN: CPKNDH ISSN: 0312-5963. Journal; General Review written in English. CAN 128:252365 AN 1998:152135 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review with 24 refs. The thymidine analog zidovudine is currently used for the treatment of HIV-infected patients, as the early development of the drug as an anticancer agent yielded modest results. A comprehensive preclin. anal., however, showed that inhibitors of de novo thymidylate synthesis, including fluorouracil and methotrexate, enhanced the antiproliferative activity of zidovudine in cancer cells. Significant inhibition of tumor growth was obtained in mice bearing human colon cancer xenografts and given i.p. zidovudine 300 to 600 mg/kg weekly in combination with methotrexate 87.5 mg/kg or i.p. fluorouracil 85 mg/kg, and in pharmacokinetic studies high peak drug plasma concns. (Cmax) of zidovudine were obtained, ranging from 610.3 to 1698.8 μmol/L. In order to exploit the therapeutic activity of zidovudine, phase I and II clin. studies were designed in combination with fluorouracil and the pharmacokinetic-pharmacodynamic profile of zidovudine was investigated. Clin. responses were obtained in patients treated i.v. with bolus fluorouracil 500 mg/m2, leucovorin and short (90 to 120 min) infusions of high dose zidovudine (up to 10 g/m2), generating drug Cmax similar to those obtained in preclin. models. However, in chemotherapy-pretreated patients receiving high dose zidovudine by the oral route (1 to 9 g/m2/day) or 48-hourly continuous i.v. infusion (2 to 20 g/m2/day) in combination with fluorouracil and leucovorin, treatment failures were obsd. despite high systemic exposure, described as the area under the plasma concn.-time curve and the occurrence of DNA strand breaks in peripheral blood mononucleated cells, the biol. expression of zidovudine activity. In conclusion, preclin. and clin. evidence suggest that the schedule of administration of zidovudine is a requisite for the expression of its activity, indicating the importance of concn.-monitored trials to optimize chemotherapy dose administration in patients.

The likelihood of tumor response appears to be related to the achievement of high peak plasma concns. of zidovudine, and const. infusions appear less likely to produce clin. results.

Answer 14:

Bibliographic Information

Continuous cell lines derived from head and neck tumors for mechanistic studies in vitro and in a nude mouse animal model. Knebel, J. W.; Eckardt, A.; Fokas, K.; Aufderheide, M.; Nolte, M. Institute of Experimental Pathology, Hannover Medical School, Hannover, Germany. International Congress Series (1996), 1114(Head and Neck Cancer: Advances in Basic Research), 111-119. Publisher: Elsevier, CODEN: EXMDA4 ISSN: 0531-5131. Journal written in English. CAN 126:54594 AN 1997:37414 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In a series of expts. the authors established and characterized continuous cell lines of different squamous cell carcinomas. The isolated cells grew in epithelial clusters and expressed cytokeratin. Their differentiation pattern and capacity differ to a certain extent. Using these in vitro systems the authors studied the effects of different chemotherapeutic drugs (e.g., MTX, 5-FU, CBDCA and Taxol). Injection of HN SCC-001 cells into nude mice gave rise to serially transplantable s.c. tumors. The cell line as well as the xenotransplants showed the phenotype and genotype characteristics of the primary tumor.

Answer 15:

Bibliographic Information

Phase II trial of edatrexate in patients with metastatic colorectal cancer. Clamon, Gerald H.; Riggs, Charles E. Jr.; Dreicer, Robert; Hohl, Raymond J. College Medicine, University Iowa, Iowa, IA, USA. Investigational New Drugs (1996), Volume Date 1995-1996, 13(4), 359-361. Publisher: Kluwer, CODEN: INNDDK ISSN: 0167-6997. Journal written in English. CAN 125:185180 AN 1996:532232 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Edatrexate is an analog of methotrexate which in vitro demonstrated activity against human colon cancer xenografts grown in nude mice. In a phase II trial, 12 patients with metastatic colorectal cancer and no prior chemotherapy were treated with Edatrexate 80 mg/m2/wk for an initial period of 8 wk. No objective responses were obsd. Edatrexate is inactive against colon cancer at the dose and schedule used in this trial.

Answer 16:

Bibliographic Information

In vivo/in vitro correlation of xenografts in nude mice and the ATP-cell viability assay. Perras, James P.; Hurst, Josephine. School Medicine, University Miami, Miami, FL, USA. Contributions to Gynecology and Obstetrics (1994), 19(Chemosensitivity Testing in Gynecologic Malignancies and Breast Cancer), 122-131. Publisher: Karger, CODEN: CGOBD6 ISSN: 0304-4246. Journal written in English. CAN 125:131526 AN 1996:450444 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors compare in vitro results of an ATP cell viability assay (ATP-CVA) to the in vivo chemosensitivity of transplanted ovary and breast xenografts in nude mice. This approach not only allows a comparison between the in vitro and in vivo systems, but it also provides a means to compare responses using multiple tumor specimens to evaluate the reproducibility of the ATP- CVA. The results strongly indicate that the ATP-CVA in vitro chemosensitivity assay provides an approach that, to a degree, approximates a clin. situation. With this method, the initial evaluations of in vitro chemosensitivity assays can be done more quickly and easily to compare with in vivo response. It has been shown for 2 xenograft tumors (ovarian and breast) that for those drugs tested, the ATP-CVA can predict the drug sensitivity of these tumors in nude mice. The reproducibility of the ATP-CVA assay is also demonstrated.

Answer 17:

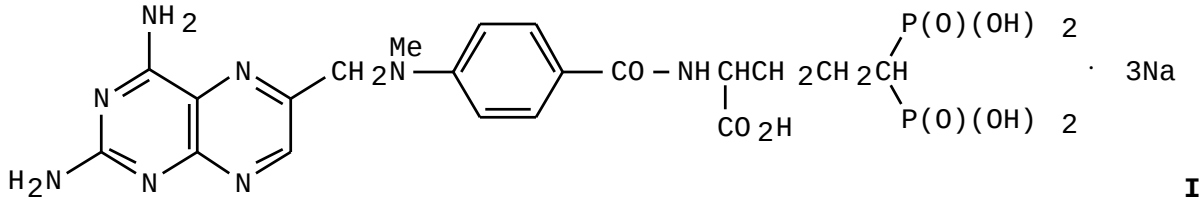
Bibliographic Information

A study of the delivery-targeting concept applied to antineoplasic drugs active on human osteosarcoma. I. Synthesis and biological activity in nude mice carrying human osteosarcoma xenografts of gem-bisphosphonic methotrexate analogs. Sturtz, G.; Appere, G.; Breistol, K.; Fodstad, O.; Schwartsmann, G.; Hendriks, H. R. Lab. Chim. Hetero-Org., Univ. Bretagne Occidentale, Brest, Fr. European Journal of Medicinal Chemistry (1992), 27(8), 825-33. CODEN: EJMCA5 ISSN: 0223-5234. Journal written in English. CAN 119:9113 AN 1993:409113 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

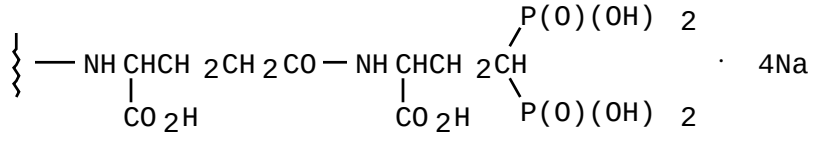
Abstract

With the aim of verifying the concept of osteotic vectorization, the synthesis of methotrexate (MTX) gem-diphosphonic analogs I, II, and III was performed. These mols. were tested on BALB/c and NIH III mice previously grafted with s.c. implants of OHS, TTX p7 and/or TTX p11 human osteosarcoma cell lines. Antineoplasic activity of II and III (active compds.) was compared to the activity for

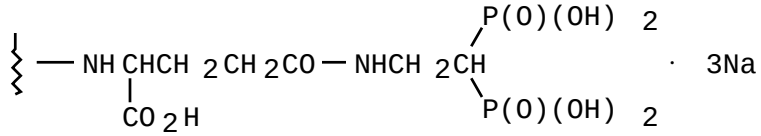
MTX alone and to activity of compd. I (inactive compd.). II and III exhibited an increased antineoplasic activity compared to MTX alone and to compd. I. At equimolar doses, II was found to be 5-6-fold more active than MTX given alone. The concept of osteotic vectorization of compd. II, which could be regarded as a prodrug, was discussed.



I



II



III

Answer 18:

Bibliographic Information

Cytotoxic analog of somatostatin containing methotrexate inhibits growth of MIA PaCa-2 human pancreatic cancer xenografts in nude mice. Radulovic, S.; Nagy, A.; Szoke, B.; Schally, A. V. Endocrine, Polypeptide Cancer Inst., Veterans Affairs Med. Cent., New Orleans, LA, USA. Cancer Letters (Shannon, Ireland) (1992), 62(3), 263-71. CODEN: CALEDQ ISSN: 0304-3835. Journal written in English. CAN 116:208105 AN 1992:208105 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Nude mice bearing xenografts of MIA PaCa-2 human pancreatic cancer cell line were treated for 4 wk with AN-51, a somatostatin octapeptide analog D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2 (RC-121) contg. methotrexate attached to the α-amino group of D-Phe in position 1. Control groups of mice received saline, RC-121 or methotrexate. Drugs were given in equimolar doses by daily s.c. injections. After 7 days of treatment with 25 μg/day of AN-51, tumor growth was completely inhibited although the treatment had to be suspended because of toxic side effects, esp. on the gastrointestinal tract, accompanied by major wt. loss of the animals. Mice were allowed to recover for 1 wk and treatment was continued with 12.5 μg/day AN-51. After 2 wk of addnl. therapy, tumor vol., percentage change in tumor vol., and tumor wts. were significantly decreased, compared with controls. Methotrexate and RC-121 also inhibited tumor growth, but their effects were not statistically significant. AN-51 retained its hormonal activity and decreased serum growth hormone levels in mice. Binding affinity of AN-51 for somatostatin receptors on MIA PaCa-2 cells was found to be 2.5-times lower than that of parent compd. RC-121. This is the first report on inhibition of human pancreatic cancer growth in vivo by somatostatin analogs carrying cytotoxic radicals.

Answer 19:

Bibliographic Information

Accumulation, intracellular metabolism, and antitumor activity of high- and low-dose methotrexate in human osteosarcoma xenografts. Meyer, William H.; Loftin, Susan K.; Houghton, Janet A.; Houghton, Peter J. Dep. Hematol. Oncol., St. Jude Children's Res. Hosp., Memphis, TN, USA. Cancer Communications (1990), 2(6), 219-29. CODEN: CNCMET ISSN: 0955-3541.

Journal written in English. CAN 115:270103 AN 1991:670103 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

High doses of methotrexate with leucovorin rescue are routinely used in the treatment of patients with osteosarcoma; the rationale for this application is controversial. Using human osteosarcoma xenografts growing in mice as a clin. relevant model, the authors compared the accumulation, intracellular metab., and tumor response of methotrexate administered as either high-dose (2400 mg/kg) or low-dose (150 mg/kg) infusions. The high-dose regimen, which included i.v. hydration and leucovorin rescue, resulted in plasma a methotrexate levels that approximated those in patients receiving the drug at 12 g/m2. The low-dose infusion produced essentially the same toxicity as the higher dose level, without use of leucovorin. The HxOs33 tumor line was moderately sensitive to the high-dose infusion (55-day delay in tumor vol. doubling time), whereas the second line, HxOs2, did not respond. Neither xenograft had a measurable response to low-dose methotrexate. Methotrexate was present in both tumors for up to 72 h post-infusion, regardless of the dosage regimen. Only shorter-chain polyglutamates (MTXglu2 and MTXglu3) were detected over this period in the high-dose trial, and levels of these derivs. were uniformly higher in the resistant HxOs2 xenograft. Low-dose infusions were assocd. with formation of longer-chain polyglutamate species, with more abundant prodn. in the HxOs2 line. Methotrexate polyglutamates exceeded baseline [3H]MTX binding of dihydrofolate reductase, as measured in tumor homogenates, at all testing intervals through 72 h in both tumor lines. Nonetheless, high-dose methotrexate-induced suppression of [14C]formate incorporation into DNA was greater in the drug-sensitive HxOs33 tumor than in HxOs2. These results suggest a therapeutic advantage for high-dose methotrexate regimens in the treatment of human osteosarcoma but show that formation of tumor MTX polyglutamates is not the sole determinant of response to this agent.

Answer 20:

Bibliographic Information

Comparative studies on the activity of methotrexate and the analog 10-deazaaminopterin (10-EDAM) against head and neck carcinoma cell lines and xenografts. Braakhuis, B. J. M.; Van Dongen, G. A. M. S.; Brown, D. H.; Snow, G. B.; Peters, G. J. Dep. otolaryngol., Free Univ. Hosp., Amsterdam, Neth. Editor(s): Curtius, Hans-Christoph; Ghisla, Sandro; Blau, Nenad. Chem. Biol. Pteridines, 1989 Proc. Int. Symp. Pteridines Folic Acid Deriv., 9th (1990), Meeting Date 1989, 1027-30. Publisher: de Gruyter, Berlin, Fed. Rep. Ger CODEN: 57FTAQ Conference written in English. CAN 115:222877 AN 1991:622877 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In exptl. human squamous cell carcinoma of the head and neck, 10-ethyl-10-deazaaminopterin had greater inhibitory activity in vitro and in vivo (as xenografts in nude mice) than methotrexate.

Answer 21:

Bibliographic Information

Mechanisms underlying methotrexate inactivity in human head and neck cancer xenografts. Braakhuis, B. J. M.; Van Dongen, G. A. M. S.; Snow, G. B.; Peters, G. J.; Leyva, A.; Jansen, G. Dep. Otolaryngol., Free Univ. Hosp., Amsterdam, Neth. Editor(s): Curtius, Hans-Christoph; Ghisla, Sandro; Blau, Nenad. Chem. Biol. Pteridines, 1989 Proc. Int. Symp. Pteridines Folic Acid Deriv., 9th (1990), Meeting Date 1989, 1119-22. Publisher: de Gruyter, Berlin, Fed. Rep. Ger CODEN: 57FTAQ Conference; General Review written in English. CAN 115:149562 AN 1991:549562 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The mechanism underlying methotrexate activity or lack thereof in a relevant in vivo model, i.e. human head and neck xenografts grown in athymic, nude mice is discussed.

Answer 22:

Bibliographic Information

Studies on chemotherapy for adenocarcinoma of the uterine cervix using xenografts transplanted in nude mice.
Yamagishi, Masaji. Fac. Med., Toyama Med. Pharm. Univ., Toyama, Japan. Nippon Sanka Fujinka Gakkai Zasshi (1991), 43(2), 165-72. CODEN: NISFAY ISSN: 0300-9165. Journal written in Japanese. CAN 115:341 AN 1991:400341 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Adenocarcinoma of the human uterine cervix was successively transplanted into nude mice and the effects of chemotherapy on adenocarcinoma of uterine cervix were investigated in this transplanted tumor. First, it was confirmed that both the original tumor and the transplanted tumor were apparently histol. the same as adenocarcinoma of the uterine cervix (endocervical type). And the transplanted tumor was shown to have the features of adenocarcinoma by an electron microscope. The doubleing time of the transplanted tumor was 9.2 days. For the chemotherapy study, first the therapeutic effects of 11 kinds of agents were screened by single-agent chemotherapy applied to the transplanted tumor. From the results of this series, 6 regimens for multi-agent chemotherapy were tried on the transplanted tumor. The effects of the chemotherapy were evaluated following Battelle Columbus Labs. Protocol and histopathol. The relative regression rates for the tumors treated with mitomycin C (MMC) + cyclophosphamide (CPM) and MMC + CPM + methotrexate (MTX) were 72.99 and 80.9% (Tn/To = 0.84), resp. The results suggest that the combinations of MMC + CPM or MMC + CPM + MTX are regimens that are possibly effective on the adenocarcinoma of human uterine cervix and are worth be trying clin.

Answer 23:

Bibliographic Information

Activity of the folate analog 10-ethyl, 10-deaza-aminopterin (10-EdAM) against human head and neck cancer xenografts.
Brown, Dale H.; Braakhuis, Boudewijn J. M.; Van Dongen, Guus A. M. S.; Van Walsum, Marijke; Bagnay, Marian; Snow, Gordon B. Dep. Otolaryngol./Head Neck Surg., Free Univ. Hosp., Amsterdam, Neth. Anticancer Research (1989), 9(6), 1549-52. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 112:171922 AN 1990:171922 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor activity of 10-Et, 10-deaza-aminopterin (10-EdAM) as compared to methotrexate (MTX) in vivo in athymic nude mice bearing head and neck squamous cell carcinoma (HNSCC) xenografts was studied. Using a schedule of 125 mg/kg i.p. for both drugs, injected on day 0 and 7, 10-EdAM caused a significant response in 2 out of 5 tumor lines, whereas MTX was completely inactive. These two lines moderately sensitive to 10-EdAM were not affected when the drug was given daily 5 times at an equitoxic dose of 0.75 mg/kg, indicating that the effect of the drug may be schedule dependent.

Answer 24:

Bibliographic Information

Therapy-induced drug resistance in a human leukemia line (LALW-2). A clinically relevant model. White, Les; Haber, Michelle; Brian, Michael J.; Norris, Murray D.; Trickett, Annette; Sosula, Leo; Tiley, Campbell; Stewart, Bernard W. Child. Leukaemia Cancer Res. Unit, Prince of Wales Child. Hospital, Sydney, Australia. Cancer (New York, NY, United States) (1989), 63(11), 2103-10. CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 111:50044 AN 1989:450044 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A human leukemic T-cell line, LALW-2, established by xenografting in nude mice, has been maintained through 14 serial passages. The cells display consistent morphol. features, immunophenotype, and karyotypic aberrations (including an 11;14 translocation) and exhibit rearrangement of the T-cell receptor β-chain gene. The growth rate of LALW-2 xenografts was differentially affected by drugs administered to host mice, the cells being resistant to cytotoxic agents (particularly methotrexate and doxorubicin) used in treatment of the donor patient. In short-term in vitro culture, LALW-2 cells exhibited extreme resistance to methotrexate and were also resistant to vincristine, vinblastine, dactinomycin, and doxorubicin. The findings differ from those obtained with lab.-derived methotrexate or multidrug-resistant cell lines. The response of LALW-2 cells, in both the nude mouse model and in vitro, is consistent with acquisition of drug-resistance as a result of clin. treatment.

Answer 25:

Bibliographic Information

Combined effects of UFT with other anticancer agents using in vivo chemosensitivity tests. Nishiyama, Masahiko; Niimi, Ken; Takagami, Shinichi; Hirabayashi, Naoki; Yamaguchi, Masahiro; Saeki, Toshiaki; Yoshinaka, Ken; Dian-Chang, Wang; Niimoto, Minoru; Hattori, Takao. Res. Inst. Nucl. Med. Biol., Hiroshima Univ., Hiroshima, Japan. Japanese Journal of Surgery (1988), 18(1), 93-7. CODEN: JJSGAY ISSN: 0047-1909. Journal written in English. CAN 109:389 AN 1988:400389 CAPLUS

Abstract

The combined and tumor activity of UFT (tegafur-uracil mixt. 1:4 molar ratio) and other anticancer agents (mitomycin C, 5-fluorouracil, adriamycin, methotrexate, and cis-diamminedichloroplatinum) were studied against 3 human tumor xenografts in a nude mouse exptl. system and in a subrenal capsule assay. The effectiveness of the combination of UFT and mitomycin C was shown in both assays against all tumor xenografts tested.

Answer 26:

Bibliographic Information

Experimental studies on heterotransplantation of human squamous cell carcinoma in nude mice and sensitivity test for anticancer agents. Sakamoto, Tomoji. Dent. Coll., Hiroshima Univ., Hiroshima, Japan. Hiroshima Daigaku Shigaku Zasshi (1987), 19(1), 1-13. CODEN: HUDJAN ISSN: 0046-7472. Journal written in Japanese. CAN 107:228638 AN 1987:628638 CAPLUS

Abstract

The antitumor effect of the chemotherapeutic agents bleomycin, peplomycin, mitomycin C, cisplatin, 5-fluorouracil, and methotrexate against human squamous cell carcinoma was evaluated in nude mice heterotransplanted with the human carcinoma. Results indicated that the sensitivity test for anticancer agents in nude mice is closely related to their clin. effectiveness. The true pos. and neg. antitumor effects of the drugs tested were 60 and 100%, resp.

Answer 27:

Bibliographic Information

Site-selective methotrexate-antibody conjugates yield a superior therapeutic effect in tumor xenograft-bearing nude mice. Lopes, A. Dwight; Radcliffe, Robert D.; Coughlin, Daniel J.; Lee, L. Stanford; McKearn, Thomas J.; Rodwell, John D. Cytogen Corp., Princeton, NJ, USA. International Congress Series (1987), 718(Clin. Immunol.), 303-7. CODEN: EXMDA4 ISSN:

0531-5131. Journal written in English. CAN 107:228555 AN 1987:628555 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Site-selective methotrexate (I)-antibody conjugates, obtained by conjugation of I to antibodies in which the oligosaccharide moiety is oxidized to aldehyde, provide better therapeutic action in treatment of tumorigenesis (nude mice with tumor xenograft) than that with conventional conjugates in which I is coupled to the lysine side chain.

Answer 28:

Bibliographic Information

Combination chemotherapy with three or four drugs on human breast and gastrointestinal cancer xenografts in nude mice (II). Fujita, Fumiko; Fujita, Masahide; Sakamoto, Yasuo; Shimozuma, Kojiro; Inaba, Hiizu; Taguchi, Tetsuo. Res. Inst. Microb., Osaka Univ., Osaka, Japan. Gan to Kagaku Ryoho (1987), 14(5, Pt. 1), 1252-9. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 107:126597 AN 1987:526597 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Combined applications of 4 drugs, vindesine (VDS), methotrexate (MTX), cisplatin (CDDP) and 5'-DFUR (5'-deoxy-5-fluorouridine) against 3 lines of human breast cancer (H-62, H-31, H-71), and one line each of gastric cancer (H-55) and colon cancer (H-110) xenografted into nude mice were evaluated in comparison with CAF (cyclophosphamide, adriamycin and 5-fluorouracil (5-FU) therapy which is commonly used for breast cancer. Combination therapy with 3 drugs (VDS, CDDP and 5'-DFUR) or 4 drugs (VDS, CDP, MTX and 5'-DFUR) achieved a marked effect with tumor shrinkage in 3 lines of tumors (H-55, H-31 and H-62). Moreover, remarkable effects were shown even in the other 2 lines which were insensitive to every single-agent therapy. A synergistic effect was obtained in 3 of the 5 lines examd. These combination therapies were histol. superior to therapies employing single-drug or CAF therapy. The side effects for combination of these 3 or 4 drugs evaluated by body wt. loss were transient and equiv. to maximal dose of VDS or CDCP.

Answer 29:

Bibliographic Information

Therapeutic effect of 5-aza-2'-deoxycytidine in human head and neck tumor xenografts. Braakhuis, Boudewijn J. M.; Leyva, Albert; Pinedo, Herbert M.; Snow, Gordon B. Dep. Otolaryngol., Free Univ. Hosp., Amsterdam, Neth. Editor(s): Rygaard, Joergen. Immune-Defic. Anim. Biomed. Res., Int. Workshop Immune-Defic. Anim., 5th (1987), Meeting Date 1985, 380-3. Publisher: Karger, Basel, Switz CODEN: 55YNAL Conference written in English. CAN 107:108921 AN 1987:508921 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In nude mice bearing xenografts of human head and neck tumors, 5-aza-5'-deoxycytidine retarded tumor growth, in some cases more effectively than vincristine, methotrexate, bleomycin, or 5-fluorouracil.

Answer 30:

Bibliographic Information

Unsuitability of monoclonal antibodies to oncogene proteins for antitumor drug-targeting. Embleton, M. J.; Habib, N. A.; Garnett, M. C.; Wood, C. Cancer Res. Campaign Lab., Univ. Nottingham, Nottingham, UK. International Journal of Cancer

(1986), 38(6), 821-7. CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 106:201591 AN 1987:201591 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Monoclonal antibodies (MAbs) to ras, sis, erb-B, src, myb and myc oncoproteins were evaluated for their potential to target anticancer drugs to malignant cells. Each antibody was tested for reactivity against both fixed and viable cultured human tumor cells by immunofluorescence, and all reacted against a variety of fixed tumor cell prepns. Reactions were also obsd. against fixed non-malignant cells. None, however, reacted significantly with viable cells. Two antibodies (against ras and myc proteins) were tested for their ability to localize to tumor xenografts in nude mice, and conjugates were constructed by linking these antibodies to methotrexate using human serum albumin as an intermediate carrier. Neither antibody localized to tumor in vivo, and the methotrexate conjugates were not significantly cytotoxic for tumor cells in vitro, in contrast to similar conjugates simultaneously prepn. with a proven antitumor MAb (79IT/36). Thus, currently available MAbs to oncogene proteins are not suitable vectors for targeting cytotoxic agents to tumor cells.

Answer 31:

Bibliographic Information

Fluorometric high-performance liquid chromatographic analysis of 10-deazaaminopterin, 10-ethyl-10-deazaaminopterin, and known metabolites. Kinahan, James J.; Samuels, Lawrence L.; Farag, Fouad; Fanucchi, Michael P.; Vidal, Pedro M.; Sirotnak, Francis M.; Young, Charles W. Clin. Pharmacol. Lab., Meml. Sloan-Kettering Cancer Cent., New York, NY, USA. Analytical Biochemistry (1985), 150(1), 203-13. CODEN: ANBCA2 ISSN: 0003-2697. Journal written in English. CAN 103:189076 AN 1985:589076 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antifolate compds. 10-deazaaminopterin (10-dAM) [52454-37-2] and 10-ethyl-10-deazaaminopterin (10-EdAM) [80576-83-6] are therapeutically superior to methotrexate in transplanted murine tumor systems and in human tumor xenografts growing in immunodeficient nude mice. The increased therapeutic index of these analogs correlates with their selective uptake, retention, and polyglutamation within neoplastic cells. A fluorescence high-performance liq. chromatog. assay applicable to 10-dAM, 10-EdAM, their polyglutamate anabolites, and their 7-hydroxy (7-OH) and deglutamate catabolites was developed. The assay is based upon the high native fluorescence of pteridine-contg. compds. which contain carbon in the 10 position. The assay employs a reverse-phase C-18 column and an ascending acetonitrile gradient in 50 mM phosphate, pH 7.0. The compds. are extd. from plasma and urine with 95% and 98% recoveries, resp., using C-18 Sep-Paks. The linear range of the assay is, for 10-dAM, 2-100 nM, and for 10-EdAM, 1-100 nM. Polyglutamated metabolites of [3H]10-EdAM isolated from L1210 cells have been sepd. by HPLC with identification of 5 derivs. (Glu 1-5) confirmed by enzymic peak shift using serum conjugase and by quant. correlation of fluorescence intensity, radioactivity, and titrn. inhibition of dihydrofolate reductase. The assay has been used successfully in pharmacokinetic analyses of plasma and urine samples from patients receiving 10-dAM and 10-EdAM. In patients who had received 10-EdAM, 7-OH-10-EdAM, and the deglutamate catabolite were also detected. This HPLC fluorescence assay is superior to the dihydrofolate reductase inhibition and binding assays with regard to specificity and precision; moreover, it can provide a means for simultaneous assay of the physiol. important anabolites and catabolites of these new antifolates.

Answer 32:

Bibliographic Information

New folate analogs of the 10-deazaaminopterin series: markedly increased antitumor activity of the 10-ethyl analog compared to the parent compound and methotrexate against some human tumor xenografts in nude mice. Schmid, F. A.; Sirotnak, F. M.; Otter, G. M.; DeGraw, J. I. Lab. Mol. Ther., Mem. Sloan-Kettering Cancer Cent., New York, NY, USA. Cancer Treatment Reports (1985), 69(5), 551-3. CODEN: CTRRDO ISSN: 0361-5960. Journal written in English. CAN 103:265 AN 1985:400265 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effect of 2 new folate analogs in the 10-deazaaminopterin series was examd. for antitumor activity against a group of human tumor xenografts in nude mice. In all 3 xenograft models studied, MX-1 mammary carcinoma, LX-1 lung carcinoma, and CX-1 colon carcinoma, 10-deazaaminopterin was minimally active, while methotrexate was inactive. In contrast, against the MX-1 and LX-1 tumors, 10-ethyl-10-deazaaminopterin [80576-83-6] at or near the LD10 dose (2-4.5 mg/kg) given once per day × 5 produced frank regressions. Activity of this analog against the CX-1 tumor was less, but retardation of tumor growth was obsd. with some minor regressions.

Answer 33:

Bibliographic Information

Sequential methotrexate (MTX) and 5-fluorouracil (FU) in human tumor xenografts. Wayss, K.; Herrmann, R.; Mattern, J.; Volm, M. Inst. Exp. Pathol., Ger. Cancer Res. Cent., Heidelberg, Fed. Rep. Ger. Medical Oncology and Tumor Pharmacotherapy (1985), 2(1), 27-32. CODEN: MOTPE2 ISSN: 0736-0118. Journal written in English. CAN 102:214740 AN 1985:214740 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Human and animal tumor lines heterotransplanted in nude mice were treated with methotrexate (MTX) [59-05-2] and 5-fluorouracil (FU) [51-21-8] sequentially. In order to investigate the relationship between tumor response and drug toxicity sequence, time and dose of both MTX and FU were varied. Pretreatment with MTX followed by FU at intervals of 3 or 24 h produced superior therapeutic results as compared with single administration of MTX or FU, simultaneous treatment, or the reverse sequence. In the MTX followed by FU regimen, dose redn. of either MTX or FU tended to decrease the antitumor effect. To investigate the toxic effects of different regimens, tumor-free nude mice were treated with MTX and FU the same way as the tumor-bearing animals. In this case, toxicity (wt. loss, leukopenia) was more pronounced in those schedules with the best therapeutic results. However, toxicity appears to be more clearly related to the applied FU dose.

Answer 34:

Bibliographic Information

Differential characteristics of two newly established human breast carcinoma cell lines. Chu, Ming Y.; Hagerty, Matthew G.; Wiemann, Michael C.; Tibbetts, Lance M.; Sato, Seiji; Cummings, Frank J.; Bogaars, Hendrik A.; Leduc, Elizabeth H.; Calabresi, Paul. Dep. Med., Roger Williams Gen. Hosp., Providence, RI, USA. Cancer Research (1985), 45(3), 1357-66. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 102:129730 AN 1985:129730 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Two human breast carcinoma cell lines, EP and MW, were established in culture from malignant pleural effusions. In addn. to producing tumors in antithymocyte serum-immunosuppressed mice, both cell lines showed epithelial characteristics and anchorage-independent growth in soft agar. EP and MW differed in morphol. (spindle-shaped vs. round), chromosomal mode (hyperdiploid vs. near triploid), estrogen receptor content (43.8 vs. 5.1 fmol/mg protein), cloning efficiency (0.24 vs. 15%), and activities (milliunits/106 cells) of creatine phosphokinase (25.7 vs. 62.6) and lactate dehydrogenase (346.7 vs. 778.5). Electron microscopy revealed that MW cells had more perinuclear filamentous material and more frequent intracytoplasmic vacuole formation than did EP cells. While having no effect on MW cells at the concns. studied (10-5 to 10-11 M), β-estradiol (10-7 M) stimulated the growth of EP cells by 106% over the hormone-depleted control. In a variety of systems, EP was consistently the more drug-sensitive of the 2 lines. In vitro, EP was significantly more sensitive to methotrexate, vincristine, and 5-fluorouracil, resp. In antithymocyte serum-mouse xenografts, EP displayed a greater response to 3 different dosages of a combination of cyclophosphamide, methotrexate, and 5-fluorouracil. One such dosage (cyclophosphamide, 32.0 mg/kg/day; methotrexate, 13.0 mg/kg/day; 5-fluorouracil, 190.0 mg/kg/day; for 1 day) reduced EP and MW tumor wts. to 5.9 and 41% of controls, resp. These results correlated well with the

clin. responses.

Answer 35:

Bibliographic Information

Use of an anti-tumor monoclonal antibody for targeting methotrexate. Embleton, M. J.; Garnett, M. C.; Baldwin, R. W. Cancer Res. Campaign Lab., Univ. Nottingham, Nottingham, UK. Protides of the Biological Fluids (1985), Volume Date 1984, 32 429-31. CODEN: PBFPA6 ISSN: 0079-7065. Journal written in English. CAN 102:105871 AN 1985:105871 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Methotrexate was conjugated to a monoclonal antibody (791T/36) to human osteogenic sarcoma cells by means of a human serum albumin bridge. The conjugate was cytotoxic in vitro to human tumor target cells which bind the antibody, but had much lower activity against antigenically non-crossreactive target cells. Free methotrexate, by comparison, was indiscriminately toxic to all target cell lines. In accordance with the lack of toxicity for cells which do not react with 791T/36 antibody, the conjugate had a therapeutic effect in vivo superior to that of free methotrexate against osteogenic sarcoma xenografts in immune-deprived mice, without evidence of host toxicity which was obsd. using the free drug at equiv. doses.

Answer 36:

Bibliographic Information

Screening test of antitumor agents by human tumor cell lines in nude mice in ascitic form. Kitahara, Takeshi; Minato, Keisuke; Shimoyama, Masanori. Natl. Cancer Cent. Hosp., Japan. Gan no Rinsho (1984), 30(9), 1158-67. CODEN: GANRAE ISSN: 0021-4949. Journal written in Japanese. CAN 102:17008 AN 1985:17008 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Human breast cancer and leukemic cells implanted in nude mice appeared to be useful models for the screening of neoplasm inhibitors. The sensitivities of implanted tissues to drugs were similar to those found in patients. Studies on the suitable route of administration in these mice provide the best administration routes for humans.

Answer 37:

Bibliographic Information

Chemotherapy and radiation therapy of human medulloblastoma in athymic nude mice. Friedman, Henry S.; Schold, S. Clifford, Jr.; Varia, Mahesh; Bigner, Darell D. Med. Cent., Duke Univ., Durham, NC, USA. Cancer Research (1983), 43(7), 3088-93. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 99:63962 AN 1983:463962 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The human medulloblastoma cell line TE-671 was grown s.c. and intracranially in athymic nude mice. Tumor-bearing animals treated with chemotherapeutic agents or radiation were compared to untreated tumor-bearing controls. Tumors growing s.c. were sensitive to cyclophosphamide [50-18-0] and vincristine [57-22-7] with growth delays in duplicate trials of 15.8/16.5 and 12.9/15.0 days, resp. These tumors were minimally responsive to the 2,5-bis(1-aziridinyl)-3,6-dioxodiethyl ester of 1,4-cyclohexadiene-1,4-dicarbamic acid

[57998-68-2] and cis-diamminedichloroplatinum II [15663-27-1] and unresponsive to methotrexate [59-05-2], NSC 351521 [72732-56-0], NSC 409962 [154-93-8], and procarbazine [671-16-9]. Radiation therapy with 2500 or 1500 rads as a single fraction produced a marked response, with growth delays of 39.5 and 21.1 days, resp. Cyclophosphamide produced a significant increase in the median survival of mice with intracranial tumors. Vincristine produced a minimal increase in the median survival while no response was seen to the 2,5-bis(1-aziridinyl)-3,6-dioxodiethyl ester of 1,4-cyclohexadiene-1,4-dicarbamic acid at the dose level and schedule tested. This model system will allow further anal. of the therapeutic sensitivity of human medulloblastoma to other agents or combined-modality regimens.

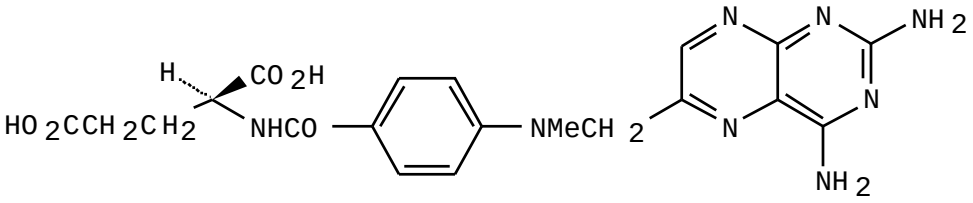
Answer 38:

Bibliographic Information

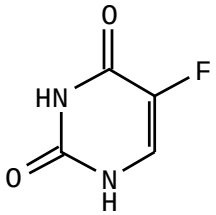
The selectivity of action of methotrexate in combination with 5-fluorouracil in xenografts of human colon adenocarcinomas. Houghton, Janet A.; Tice, Arvil J.; Houghton, Peter J. Dep. Biochem. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. Molecular Pharmacology (1982), 22(3), 771-8. CODEN: MOPMA3 ISSN: 0026-895X. Journal written in English. CAN 98:209664 AN 1983:209664 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The possibility for increasing the therapeutic index in the treatment of human colon adenocarcinomas maintained as xenografts in immune deprived mice using combinations of methotrexate (I) [59-05-2] that preceded 5-fluorouracil (II) [51-21-8] was studied. I, at a dose of 100 mg/kg, increased the 5-phosphoribosyl-1-pyrophosphate (PRPP) [7540-64-9] concn. in 3 colon xenograft lines to a max. between 14 and 24 h after treatment. In murine bone marrow, concns. of PRPP decreased progressively after I treatment, but in ileum there was a dramatic increase such that by 4 h PRPP was 968% of control. The metab. of II-63H administrated 24 h after I was increased in ileum and resulted in an increased rate and a greater level of incorporation of II-63H into RNA. Only a slight elevation in the incorporation of II-63H into the RNA of one tumor line (HxELC,2) was obsd. The scheduling of II at a dose level of 25 mg/kg 24 h after a priming dose of I (100 mg/kg) was at least as toxic as 100 mg of II/kg administered alone. The dose-limiting toxicity was related to gastrointestinal damage; no bone marrow toxicity was detected. At ≤100 mgI/kg, the increase in PRPP obtained in gastrointestinal tissue was greater than that obsd. in human colon xenografts 24 h after treatment. A basis for increasing the therapeutic efficacy of II through a selective increase in tumor PRPP using I was not obtained in these studies.



I



II

Answer 39:

Bibliographic Information

Chemotherapy of human breast-carcinoma xenografts. Bailey, M. J.; Gazet, J. C.; Smith, I. E.; Steel, G. G. Inst. Cancer Res., Sutton/Surrey, UK. British Journal of Cancer (1980), 42(4), 530-6. CODEN: BJCAAI ISSN: 0007-0920. Journal written in

English. CAN 94:95754 AN 1981:95754 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Sensitivities were varied for 5 lines of human breast carcinoma xenografts, grown and passaged in immune-suppressed mice, to cyclophosphamide [50-18-0], methotrexate [59-05-2], 5-fluorouracil [51-21-8], adriamycin [23214-92-8], vincristine [57-22-7], and melphalan [148-82-3], alone and in combination. The most effective single agent or combination differed for each tumor. This system may be useful for testing new cytotoxic agents and predicting clin. chemotherapy response.

Answer 40:

Bibliographic Information

Use of heterotransplants in diffusion chambers for determining the individual drug sensitivity of human ovarian cancer to chemotherapeutic drugs. Sobol, I. L.; Marenich, A. F. Cancer Res. Cent., Moscow, USSR. Byulleten Eksperimental'noi Biologii i Meditsiny (1979), 88(8), 243-5. CODEN: BEBMAE ISSN: 0365-9615. Journal written in Russian. CAN 91:150972 AN 1979:550972 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The sensitivity of 10 ovarian tumor heterotransplants in diffusion chambers in mice to hexamethylmelamine [645-05-6], cyclophosphane [50-18-0], 5-fluorouracil [51-21-8], methotrexate [59-05-2], dactinomycin [50-76-0], 17-hydroxyprogesterone caproate [630-56-8], and thiotepa [52-24-4] was variable. E.g., hexamethylmelamine, cyclophosphane, 5-fluorouracil, and methotrexate had a brief inhibiting effect in growth of a solid glandular cancer, inhibited growth of a glandular papillary cancer, and had no effect on growth of a papillary adenocarcinoma. In 4 of 5 cases where results of these expts. were compared with results of expts. obtained in the treatment of patients with the same drugs, exptl. results correlated with clin. findings.

Answer 41:

Bibliographic Information

Regression of human melanoma xenografts in nude mice injected with methotrexate linked to monoclonal antibody 225.28 to human high molecular weight-melanoma associated antigen. Ghose T; Ferrone S; Blair A H; Kralovec Y; Temponi M; Singh M; Mammen M Department of Pathology, Dalhousie University, Halifax, Nova Scotia, Canada Cancer immunology, immunotherapy : CII (1991), 34(2), 90-6. Journal code: 8605732. ISSN:0340-7004. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 1760821 AN 92103651 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Intravenous injections into nude mice of 5 mg/kg methotrexate (MTX) linked to the antibody to human high molecular weight-melanoma associated antigen (HMW-MAA), monoclonal antibody (mAb) 225.28, an IgG2a, on days 1, 4, 7, 10 and 14, starting 24 h after subcutaneous inoculation of 2 x 10(6) cultured human M21 melanoma cells inhibited mean tumor volume by 90% on day 14 and by 65% on day 50 after the beginning of the treatment. Injections of equimolar amounts of free MTX and MTX linked to normal mouse IgG or to an isotype-matched myeloma protein did not inhibit tumor growth significantly. MTX linked to mAb 225.28 did not inhibit the xenograft of a subline of human melanoma cell line M21 without detectable expression of HMW-MAA. In a clonogenic assay, the MTX-225.28 conjugate was three times more potent in inhibiting the growth of M21 melanoma cells than free MTX, but did not inhibit the growth of kidney carcinoma cells Caki-1, which do not express high-Mr MAA. In contrast, MTX linked to the mAb DAL K29, reacting with kidney carcinoma cells Caki-1, inhibited their growth but did not affect that of melanoma cells. M21 melanoma cells isolated from the residual tumor of a mouse treated with the MTX-225.28 conjugate did not differ in their reactivity with mAb 225.28 and in their

sensitivity to MTX when compared with M21 cells from an untreated mouse.

Answer 42:

Bibliographic Information

Comparative study of the sensitivity of head and neck cell lines to methotrexate (MTX) and the analog 10-ethyl, 10-deazaaminopterin (10-EdAM). Brown D H; Braakhuis B J; Van Dongen G A; Snow G B Department of Otolaryngology-Head and Neck Surgery, Free University Hospital, Amsterdam, The Netherlands Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery (1990), 102(1), 20-5. Journal code: 8508176. ISSN:0194-5998. (COMPARATIVE STUDY); (IN VITRO); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2106113 AN 90159689 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Squamous cell lines cultured in vitro provide a potential test system for the selection of analogs that have an improved therapeutic index. The growth inhibitory effects of methotrexate and the new folate analog 10-ethyl, 10-deazaaminopterin were compared in three in vitro-cultured human head and neck squamous cell carcinoma cell lines. The inhibitory concentrations of the new analog were 10- to 100-fold lower than the inhibitory concentrations of methotrexate. The sensitivity of these three head and neck squamous cell carcinoma cell lines to both drugs was essentially the same as the sensitivity of a rhabdomyosarcoma cell line known to be very sensitive to methotrexate when the cell line is grown as a xenograft in athymic nude mice. These data indicate that 10-ethyl, 10-deazaaminopterin may be a new and effective agent against head and neck squamous cell carcinoma.

Answer 43:

Bibliographic Information

Biodistribution and tumour localization of a methotrexate-monoclonal-antibody 791T/36 conjugate in nude mice with human tumour xenografts. Pimm M V; Clegg J A; Garnett M C; Baldwin R W Cancer Research Campaign Laboratories, University of Nottingham, UK International journal of cancer. Journal international du cancer (1988), 41(6), 886-91. Journal code: 0042124. ISSN:0020-7136. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 3372062 AN 88227059 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The blood kinetics and tumour localization of a conjugate of methotrexate (MTX) and MAb 791T/36 were examined in nude mice with human tumour xenografts. The antibody moiety of the conjugate was detected by labelling with 125I and the drug moiety was assayed using a radioimmunoassay for methotrexate. After radioiodination, the drug moiety was co-precipitable with the radiolabel when TCA or rabbit anti-mouse IgG antiserum was used. Following i.v. injection, serum kinetics of both the antibody and the drug moieties of the conjugate were essentially similar, and the integrity of serum-borne conjugate was confirmed by the co-precipitation of radiolabel and drug. The radiolabelled antibody moiety of the conjugate localized in tumour xenografts, with 5-7% of the injected dose being present per gram of tissue within 6 hr of injection, and the levels were maintained for up to 4 days. Analysis of tumour levels of the MTX moiety showed a progressive uptake over the 4-day observation period with up to 4% of the injected dose being present per gram of tumour when the experiment was terminated. Parallel studies with free MTX showed rapid clearance from the blood and a maximum of 0.35% of the dose/g of tumour 30 min after injection. Control immunoglobulin conjugated to MTX did not show tumour localization of either the antibody or the drug moieties. These studies confirm that in vivo MTX remains bound to antibody in this type of drug antibody conjugate and demonstrate site-specific targeting of this therapeutic agent.

Answer 44:

Bibliographic Information

Sequential combination chemotherapy consisting of vincristine, peplomycin, methotrexate, cis-diamminedichloroplatinum (II), cytosine arabinoside and 5-fluorouracil, for advanced urothelial cancer. Yamauchi T; Hida S; Ooishi K; Okada K; Yoshida O Hinyokika kiyo. Acta urologica Japonica (1985), 31(7), 1093-104. Journal code: 0421145. ISSN:0018-1994. (CASE REPORTS); (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2414981 AN 86047350 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Two VPM-CisCF chemotherapy regimens (vincristine (VCR), peplomycin (PEP), methotrexate (MTX), cis-diamminedichloroplatinum (II) (CDDP), cytosine arabinoside (Ara-C) and 5-fluorouracil (5-FU), established using human bladder cancer xenografts in nude mice were applied for advanced urothelial cancer. VPM-CisCF (I) consisted of 0.4 mg/m2 VCR on days 1 and 4, 2 mg/m2 PEP on days 1-7, 2 mg/m2 MTX on days 2, 3, 5 and 6, 20 mg/m2 CDDP on days 8, 20 mg/m2 Ara-C on days 8 and 13, and 150 mg/m2 5-FU on days 10-12. VPM-CisCF (II) consisted of 0.6 mg/m2 VCR on days 1 and 3, 3 mg/m2 PEP on days 1-4, 3 mg/m2 MTX on days 2 and 3, 35 mg/m2 CDDP on day 4, 20 mg/m2 Ara-C on days 4 and 7, and 200 mg/m2 5-FU on days 5 and 6. These doses were adjusted for each case: the above mentioned dose x [(80/(40 + Age))2 + (Karnofsky's performance status/100)2]. VPM-CisCF (I) was administered to 6 patients (bladder cancer and transitional cell carcinoma), intra-arterially in two cases. One patient showed a complete response and survived for 7 months, three partial response (PR) surviving for 13, 8 and 37 (arterial-infused case) months, one showed minor response (MR) surviving for 4 months, and one had no change (NC) surviving for 5 months. VPM-CisCF (II) was administered to 11 patients (1 ureteral cancer, 1 renal pelvic cancer, 9 bladder cancer, and 10 transitional cell carcinoma except a case of mixed type of transitional cell carcinoma and squamous cell carcinoma). Four of the patients who had PR survived for 9, 8, 8 and 7 (alive) months, two who had MR survived for 8 and 4 months, three who had NC survived for 6, 4 and 4 months, and who two had progressive disease survived for 8 and 6 months. The major toxicities were myelosuppression and gastrointestinal symptoms, especially nausea and vomiting, but the treatment was well-tolerated.

Answer 45:

Bibliographic Information

Lack of effect of methotrexate on human head and neck tumours transplanted in athymic nude mice. Braakhuis B J; Leyva A; Schoevers E J; Boerrigter G H; Schornagel J H; Snow G B Acta oto-laryngologica (1985), 99(3-4), 208-13. Journal code: 0370354. ISSN:0001-6489. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 4013712 AN 85247519 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Human head and neck tumour tissues derived from 16 different patients were transplanted in athymic nude mice. Treatment of tumour-bearing animals with methotrexate had little or no effect on the doubling time of the xenografts. Included were three tumour lines derived from patients in whom methotrexate did demonstrate antitumour activity. These results are also in contrast to clinical experience with methotrexate, showing remissions in 50% of patients with head and neck cancer. It is unlikely that this lack of effect of methotrexate is attributed to a difference in drug pharmacokinetics between man and nude mouse, since a xenografted rat tumour was found to be sensitive. With regard to possible resistance mechanisms underlying methotrexate inactivity, we found no evidence of increased dihydrofolate reductase activity in the methotrexate-insensitive human xenografts. It is possible that in this model a selection occurs favouring the outgrowth of a resistant subpopulation of tumour cells.